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10/700,906	11/04/2003	Benjamin Oshlack	200.1133CON5	1129

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DAVIDSON, DAVIDSON & KAPPEL, LLC
14th Floor
485 Seventh Avenue
New York, NY 10018

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,906	OSHLACK ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/26/07; 3/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Response after Non-Final Office Action, the Amendments and Applicant's Arguments/Remarks, all filed 12/26/07 and the Information Disclosure Statements (IDS) filed 12/26/07 and 03/21/08 is acknowledged.

Applicant has overcome the following rejection(s) by virtue of the amendment and/or persuasive remarks: (1) The 35 U.S.C. §102(b) rejection of claims 75-78 over Kreek et al. (USPN 4,987,136) has been withdrawn; (2) The 35 U.S.C. §102(b) rejection of claims 75, 76 & 78 over Palermo (WO 99/32120) has been withdrawn.

Claims 75-86 are pending in this action. Claims 75-78 have been amended. New claims 79-86 have been added. Claims 1-74 have previously been cancelled. Claims 75-86 remain rejected.

* * * * *

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 75 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a dosage form that is "chewed, crushed, ground, sheared or dissolved" does not reasonably provide enablement for a dosage form that is "tampered". The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The term "tampered" should instead be recited as "chewed, crushed, sheared, ground or dissolved in a solvent'. These physical actions are the only ones supported by the instant specification.

* * * * *

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 75 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation "...as compared to the dosage form that has been tampered with" is indefinite since no additional dosage form has been recited. It is unclear as to whether Applicants intend to mean "said dosage form". If so, a specific dosage formulation should be recited to show one of ordinary skill in the art what dosage form should be compared. If the Applicants mean any dosage form containing the active ingredient recited, then the prior art meets this limitation.

* * * * *

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 75-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palermo (WO 99/32120).

Palermo (WO '120) teaches an oral dosage form of an opioid analgesic, comprising an analgesically effective amount of an opioid agonist together with an opioid antagonist, the amount of opioid antagonist including being sufficient to counteract opioid effects if extracted together with the opioid agonist (see p. 6, lines 1-18).

In certain preferred embodiments, the opioid agonist is hydrocodone, hydromorphone, oxycodone, morphine or pharmaceutically acceptable salts thereof (p. 7, lines 5-6). Suitable opioid antagonists disclosed include naltrexone, naloxone, nalmephene, cyclazocine and levallorphan. A most preferred antagonist is naltrexone (p. 11, lines 14-19); (p. 13, lines 14-31). In certain preferred embodiments of the method, the opioid agonist and the opioid antagonist are combined in a ratio of opioid antagonist to opioid agonist which is analgesically effective when the combination is administered orally, but which is aversive in a physically dependent subject (p. 7, lines 7-15). In embodiments where the opioid is hydrocodone and the antagonist is naltrexone, the ratio of naltrexone to hydrocodone is preferably from about 0.03-0.27:1 by weight (p. 7, lines 15-26).

Palermo teaches that the dosage forms of the invention may be liquids, tablets, multiparticulates, dispersible powders or granules, hard or soft capsules, lozenges, aqueous or oily suspensions, emulsions, syrups, elixirs, microparticles , buccal tablets, etc. (p. 7, lines 27-31); (p. 8, line 29 – p. 9, line 1). In certain preferred embodiments, the oral dosage forms are sustained release formulations. This may be accomplished via the incorporation of a sustained release carrier into a matrix containing the opioid agonist and opioid antagonist; or via a

sustained release coating of a matrix containing the opioid agonist and opioid antagonist, where the sustained release coating contains at least a portion of the sustained release carrier included in the dosage form (p. 8, lines 1-9); (p. 20, lines 16-21).

With regards to ratios, Palermo teaches that the combinations of opioid antagonists/opioid agonists which are orally administered in ratios which are equivalent to the ratio of e.g., naltrexone to hydrocodone set forth are considered to be within the scope of the invention. For example, in some embodiments, naloxone is utilized as the opioid antagonist, the amount of naloxone included in the dosage form being large enough to provide an equiantagonistic effect as if naltrexone were included in the combination (p. 19-31). This demonstrates bioequivalency of the dosage forms.

Palermo teaches that the dosage forms may be coated with one or more materials suitable for the regulation of release or the protection of the formulation. The coatings are provided to permit either pH-dependent or pH-independent release (p.21, lines 18-29).

In preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer or (iii) mixtures thereof (p. 22, lines 6-14).

Suitable and preferred alkylcellulose polymers taught include ethylcellulose (p. 22, lines 19-25). Acrylic polymers are also disclosed and include acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid) and the like (p. 23, line 10 – p. 24, line 22); (p. 29, lines 7-18). Plasticizers can also be included in the composition (p. 24, line 24 – p. 25, line 20). A process for preparing coated beads is disclosed at p. 25, line 21 – p. 28, line 8.

Matrix bead formulations are disclosed at page 28. Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials and any pharmaceutically acceptable hydrophobic material or hydrophilic material, which is capable of imparting, controlled release of the active agent and which melts (or softens to the extent necessary to be extruded) may be used in this invention (p. 28, lines 19-30).

With regards to amounts of hydrophobic material claimed, the Examiner notes that suitable or effective amounts can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results as these are variable parameters attainable within the art. Moreover, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The Palermo reference explicitly recognizes and teaches oral dosage forms comprising opioid agonists in combination with opioid antagonists, whereby the dosage forms are effective for the substantial reduction of pain. Given the teachings of Palermo discussed above, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Claims 75-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Malley et al. (U.S. Pat. No. 6,004,970) in view of Whitmire (U.S. Pat. No. 6,120,806) OR Palermo (WO 99/32120).

O'Malley ('970) teaches an opioid antagonist composition in oral administration forms such as tablets and capsules (col. 3, lines 58-67). The opioid antagonists taught include nalmefene, naloxone, naltrexone or a mixture of any of these (col. 3, lines 1-3).

O'Malley does not teach a hydrophobic material.

Whitmire ('806) teaches an oral controlled release dosage form comprising an opioid antagonist (see Abstract). The oral dosage form comprises the opioid antagonist and hydrophobic material in a matrix form. Suitable materials are disclosed at column 10, line 37 – col. 11, line 8).

* * * * *

The teachings of O'Malley are discussed above. O'Malley does not teach a hydrophobic material.

Palermo ('120) teaches an oral dosage form of an opioid analgesic, comprising an analgesically effective amount of an opioid agonist together with an opioid antagonist, the amount of opioid antagonist including being sufficient to counteract opioid effects if extracted together with the opioid agonist (see p. 6, lines 1-18). Suitable opioid antagonists disclosed include naltrexone, naloxone, nalmephene, cyclazocine and levallorphan. A most preferred antagonist is naltrexone (p. 11, lines 14-19); (p. 13, lines 14-31). In preferred embodiments, the

substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer or (iii) mixtures thereof (p. 22, lines 6-14).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the hydrophobic materials as taught by either Whitmire or Palermo within the formulations of O'Malley. One of ordinary skill in the art would be motivated to do so with a reasonable expectation of success because both Whitmire and Palermo recognize and teach the inclusion of routinely used hydrophobic materials in their inventions, effective for their sustained release properties. The expected result would be an improved controlled release pharmaceutical dosage form for the treatment of pain.

* * * * *

Claims 75-79 and 83-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreek et al. (U.S. Pat. No. 4,987,136).

Kreek et al. ('136) teach oral sustained release dosage forms that comprise effective amounts of an opioid antagonist, such as naloxone, naltrexone, nalmefine and related compounds (col. 1, lines 59-66); (col. 2, lines 4-62).

Polymeric carriers are disclosed that include carnauba wax, cellulose esters and ethers, fats, keratin, gluten or various natural or synthetic esters (col. 5, lines 63-68). The polymeric carrier is comprised in amounts of from about 80% to 95% (col. 6, lines 58-65).

Kreek teaches sustained release forms of the medicament, which can deliver 10 to 50 mg of medicament per day and over selected periods of time, for example 4 to 12 hours (col. 2, lines 4-10).

With regards to the ratios claimed, it is the position of the Examiner that no unexpected results accrue from the instant ratios claimed, as these are variable parameters that can be attained using routine experimentation.

With respect to the claim limitations drawn to the dosage form "not posing a risk of precipitation of withdrawal" and "the opioid antagonist not being bioavailable when the dosage form is intact" (claims 83 & 84 respectively), the Examiner notes that these are future-intended use limitations, which do not accord patentable weight to the claims.

The instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, given the explicit teachings of Kreek et al.

Response to Arguments

Applicant's arguments filed 12/26/07 have been fully considered and were found to be partially persuasive.

Rejection under 35 U.S.C. 102(b) over Kreek et al. (USPN4,897,136):

Applicant argued, "The Kreek patent does not teach a dosage form comprising particles comprising "(a) a therapeutically active agent consisting essentially of an opioid antagonist and (b) means for sequestering the opioid antagonist such that the said opioid

antagonist is substantially not released when the dosage form is orally administered intact, as compared to the dosage form that has been tampered with" as recited in amended independent claim 75. Applicants respectfully note that, in the methods of the Kreek patent, the opioid antagonist is necessarily released, e.g., in the amounts "to treat gastroenterologic disorders." See, e.g., the Kreek patent, column 2, lines 27-35."

Applicant's arguments have been fully considered and were found to be persuasive based on the amendments to the claim language. Accordingly, the 35 U.S.C. §102(b) rejection over Kreek et al. has been withdrawn.

The rejection has now been reformulated as a §103(a) rejection over Kreek et al.

Rejection under 35 U.S.C. 102(b) over Palermo (WO 99/32120):

Applicant argued, "The Palermo Publication does not teach a dosage form comprising particles comprising a therapeutically effective agent consisting essentially of an opioid antagonist…and a dosage form that is substantially not released when the dosage form is orally administered intact, as compared to the dosage form that has been tampered with" as recited in amended claim 75."

Applicant's arguments have been fully considered and were found to be persuasive based on the amendments to the claim language. Accordingly, the 35 U.S.C. §102(b) rejection over Palermo has been withdrawn.

Rejection under 35 U.S.C. 103(a) over Palermo (WO '120):

Applicant argued," The Palermo Publication does not teach a dosage form comprising particles comprising a therapeutically effective agent consisting essentially of an opioid antagonist…and a dosage form that is substantially not released when the dosage form is orally administered intact, as compared to the dosage form that has been tampered with" as recited in amended claim 75."

Applicant's arguments have been fully considered, but were not deemed persuasive. The "consisting essentially of" language does not exclude the presence of the additional therapeutic ingredient (i.e., agonist) of the Palermo Publication. Applicant would further have the burden of showing that the formulation of the reference as a matrix would be detrimental to the results desired to be achieved. Given Applicant's disclosure at page 7, lines 20-31 as instantly presented Applicant cannot distinguish from the matrix of the reference. The claimed embodiments would not exclude the matrix of the reference. Arguments based on rates of release and ratios of antagonist claimed are not supported by a showing of any unusual and/or unexpected results. Furthermore, such parameters (i.e., ratios) can be determined by one of ordinary skill in the art based on routine or manipulative experimentation to obtain optimal results, as these are variable parameters. The prior art teaches the same desired result. Finally, note that the term "sequestered", even as defined by Applicant's specification, merely requires that the formulation at some point in time be non-releasable. For these reasons, the rejections of record have been maintained.

Rejection under 35 U.S.C. 103(a) over O'Malley et al. (USPN 6,004,970) in view of Whitmere (USPN 6,120,806) OR Palermo (WO '120):

Applicant argued," The O'Malley patent describes treatment of nicotine dependency by administration of an opioid antagonist. O'Malley does not teach or suggest a means for sequestering the opioid antagonist such that the said opioid antagonist is substantially not released when the dosage form is orally administered intact, as compared to the dosage form that has been tampered with" as recited in amended claim 75."

Applicant's arguments have been fully considered, but were not deemed persuasive. Applicant's argument that "O'Malley does not teach an opioid antagonist that is substantially not released when the dosage form is orally administered intact, as compared to the dosage form that has been tampered with" was not deemed persuasive as the limitation presented by Applicant is drawn to a future-intended use of the composition, which accords no patentable weight to the claims. The O'Malley reference vividly teaches a formulation and treatment method directed to the administration of an opioid antagonist, provided as the primary active ingredient. Moreover, Applicant's arguments based on rates of release and/or ratios of antagonist claimed are not supported by a showing of any unusual and/or unexpected results. Furthermore, such parameters (i.e., ratios) can be determined by a skilled artisan via routine experimentation. Finally, note that the term "sequestered", even as defined by Applicant's specification, merely requires that the formulation at some point in time be non-releasable. For these reasons, the rejections of record have been maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley, can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Humera N. Sheikh/

Primary Examiner, Art Unit 1618

hns

March 31, 2008